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Cognitive enhancers for facilitating drug cue extinction: Insights from animal models

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ABSTRACT

Given the success of cue exposure (extinction) therapy combined with a cognitive enhancer for reducing anxiety, it is anticipated that this approach will prove more efficacious than exposure therapy alone in preventing relapse in individuals with substance use disorders. Several factors may undermine the efficacy of exposure therapy for substance use disorders, but we suspect that neurocognitive impairments associated with chronic drug use are an important contributing factor. Numerous insights on these issues are gained from research using animal models of addiction. In this review, the relationship between brain sites whose learning, memory and executive functions are impaired by chronic drug use and brain sites that are important for effective drug cue extinction learning is explored first. This is followed by an overview of animal research showing improved treatment outcome for drug addiction (e.g. alcohol, amphetamine, cocaine, heroin) when explicit extinction training is conducted in combination with acute dosing of a cognitive-enhancing drug. The mechanism by which cognitive enhancers are thought to exert their benefits is by facilitating consolidation of drug cue extinction memory after activation of glutamatergic receptors. Based on the encouraging work in animals, factors that may be important for the treatment of drug addiction are considered.

In the anxiety disorders field, numerous studies have shown that exposure therapy, a procedure involving repeated confrontation with feared stimuli in a controlled setting, is highly effective as a stand-alone treatment for reducing anxiety and preventing its return (Hofmann et al., 2009; Otto et al., 2004). Exposure therapy for substance use disorders is conceptually similar in that in a controlled setting, individuals addicted to drugs are confronted repeatedly with drug cues. This approach, however, is not consistently effective in reducing reactivity to drug cues and for preventing drug relapse (Conklin and Tiffany, 2002). Several factors may undermine the efficacy of exposure therapy for substance use disorders, but we suspect that neurocognitive impairments associated with chronic drug use, particularly in individuals who are most severely dependent, are an important contributing factor. Exposure therapy is a form of extinction learning, and it is noteworthy that the brain sites needed for effective extinction learning may become dysfunctional after chronic drug use (Fowler et al., 2007; Stephens and Duka, 2008; Liu et al., 2009; for review, see Kantak and Nic Dhonnchadha, 2011). One focus of the current review is on animal research models that explore the relationship between brain sites whose learning, memory and executive functions are impaired by chronic drug use and brain sites that are important for effective drug cue extinction learning. While neurocognitive impairments may undermine extinction learning, new hope is afforded by preclinical research, reviewed below, showing improved treatment outcome for drug addiction when explicit extinction training is conducted in combination with acute (single injection) or subacute (two or more injections) dosing with a cognitive-enhancing drug. It is hoped that employment of this dosing regimen will avoid potential confounds such as sensitization of the gluatamatergic system due to repeated administration over short intervals (Boje et al., 1993; Parnas et al., 2005; Botreau et al., 2006; Werner-Seidler and Richardson, 2007) that may diminish the efficacy of the particular cognitive enhancer in use. In this respect, the use of cognitive enhancers for the treatment of substance use disorders differs conceptually from their use in the treatment of other neuropsychiatric disorders (e.g., Alzheimer's, Schizophrenia, and Attention Deficit/Hyperactivity Disorder) where a chronic rather than an acute dosing regimen would be employed.

1. Neurocognitive deficits associated with abused substances

The close correspondence in the neurocognitive deficits produced by abused substances in humans and animals suggests that meaningful insights can be obtained from animal models of drug-related learning and modification by pharmacological agents. One advantage of conducting animal studies is that they allow systematic assessment of the effects of drugs of abuse on neurocognitive function throughout the lifespan. Studies in animals include work on attention, working memory and impulsivity (prefrontal cortex-related functions) as well as work on associative learning and memory (amygdala- and hippocampus-related functions) following exposure to several drugs

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of abuse (*e.g.,* cocaine, amphetamine, opiates, ethanol and nicotine). Below, distinctions are made as to whether drugs were administered acutely or chronically, whether drugs were administered contingently (self-administered) or non-contingently (experimenter-delivered injections or passively yoked delivery), and whether animals were tested in the drug-free state or while under the influence of drug. The mode of drug delivery may be an important factor for observing neurocognitive changes because numerous animal studies report a variety of physiological and neurochemical distinctions between contingent and noncontingent drug exposure (Kantak et al., 2005; Udo et al., 2004).

1.1. Attention

Chronic cocaine injection during the prenatal period in rats has been shown to disrupt both selective and sustained attention during adulthood (Garavan et al., 2000; Gendle et al., 2003). Likewise, adolescent rats given repeated injections of cocaine were shown to display abnormally rapid shifts in selective attention during adulthood (Black et al., 2006). When cocaine and other drugs of abuse such as amphetamine and heroin are contingently self-administered by adult rats and then withdrawn, deficits in sustained attention have been found as well (Dalley et al., 2005; 2007). Chronic amphetamine injection additionally produces deficits in selective and sustained attention in adult rats (Crider et al., 1982; Fletcher et al., 2007). Interestingly, acute cocaine or amphetamine injection in adult rats was found to improve selective and sustained attention (Bizarro et al., 2004; Grilly et al., 1989; Koffarnus and Katz, 2010) and to reduce variance in the amplitudes of auditory evoked potentials (Robledo et al., 1993). These effects are consistent with the masking of attention deficits after recent cocaine use in dependent individuals (Pace-Schott et al., 2008; Woicik et al., 2009). In a study examining the effects of acute nicotine, acute ethanol and their combination on sustained attention in adult rats, it was demonstrated that nicotine alone improved attention and that ethanol alone slightly disrupted attention, but that both drugs combined produced large decrements in attention (Bizarro et al., 2003). In other studies of sustained attention, it was shown that acute ethanol injection at a dose that did not impair attention was able to block the improvement in attention induced by an acute injection of nicotine (Rezvani and Levin, 2003). As nicotine and ethanol often are taken together by humans (Hughes, 1995), their combined use may result in suboptimal attention. Interestingly, daily exposure to ethanol vapor for 14 days was shown to improve the accuracy of sustained attention in adolescent and adult rats, which may have been due to central nervous system arousal induced by the ethanol vapor (Slawecki, 2006). Collectively, these studies suggest that while acute exposure to certain drugs may improve attention, chronic exposure to drugs such as cocaine, amphetamine and opiates disrupts attention. These disruptions in attention appear to be related to the direct pharmacological effects of these drugs of abuse as there are similar effects of contingent and non-contingent drug exposure.

1.2. Working memory

In rat models, chronic nicotine infusion was shown to improve working memory (Levin et al., 1996). However, during the two weeks after withdrawal, nicotine-induced improvements in working memory were no longer evident. Regarding other drugs of abuse, working memory deficits are reported in rats trained to self-administer cocaine (Kantak et al., 2005) and trained to self-administer cocaine and then withdrawn (Harvey et al., 2009; George et al., 2008). Interestingly, passively yoked cocaine delivery did not impact working memory (Harvey et al., 2009; Kantak et al., 2005), suggesting that the contingency of cocaine delivery is important for altering the working memory function of the prefrontal cortex. Although acute injection of amphetamine improves working memory (Meneses et al., 2011), chronic injection of amphetamine neither improves nor disrupts working memory (Shoblock et al., 2003), suggesting that contingency of amphetamine delivery may be a factor as well with repeated exposure. Regarding opiates, rats made dependent on morphine displayed deficits in working memory if i.p. injections were given (Braida et al., 1994), but not if oral solutions were provided (Miladi et al., 2008). These findings suggest that non-contingent morphine exposure produces inconsistent effects on working memory. How working memory in rats may be impacted by contingent morphine exposure is not yet known. In contrast, before and after withdrawal from chronic ethanol injection or its oral consumption, working memory deficits are apparent (Santin et al., 2000; Santucci et al., 2004; White et al., 2000). Thus, ethanol may be disruptive to working memory due to its direct pharmacological action. Interestingly, nicotine plus ethanol co-injection in rats produces pronounced deficits in working memory at doses of each that do not alter working memory when injected alone (Rezvani and Levin, 2003).

1.3. Impulsivity

While impulsivity is a risk factor that predicts vulnerability for drug abuse, it also is a consequence of chronic drug use (Carroll et al., 2009; Winstanley et al., 2010). Impulsivity is associated with a number of drugs of abuse. In animal studies, chronic cocaine injection (Paine et al., 2003) and acute morphine injection (Kieres et al., 2004; Pattij et al., 2009; Pitts and McKinney, 2005) have been shown to increase impulsivity in a delayed discounting task. Notably, chronic cocaine self-administration in rats prescreened for low impulsivity can cause these rats to become more impulsive on a delayed discounting task for food after cocaine is withdrawn (Anker et al., 2009). Rats with low impulsivity also are more impulsive after acute amphetamine injection (Perry et al., 2008) and withdrawal from chronic amphetamine self-administration additionally increases impulsivity in rats (Dalley et al., 2007). In rats chronically injected with nicotine during adolescence or adulthood and then withdrawn for 5 weeks, impulsive choice for immediate small food rewards over delayed large food rewards was not observed (Counotte et al., 2009). However, in another study of chronic nicotine injection, adult rats responded more impulsively in a delayed discounting task for up to 30 days after nicotine was withdrawn (Dallery and Locey, 2005). These findings suggest that the nicotine deprivation effect on impulsive choice is associated mainly with the early stages of nicotine withdrawal.

Rats and mice selectively bred for high ethanol-preference were shown to be more impulsive than their counterparts selectively bred for low ethanol-preference, consistent with the idea that impulsivity is a trait characteristic of alcoholism (Oberlin and Grahame, 2009; Wilhelm and Mitchell, 2008). However, acute ethanol injection in an outbred rat strain was shown to produce increased impulsivity. Rats chose immediate rewards over delayed rewards, suggesting induction of impulsivity by ethanol exposure (Olmstead et al., 2006). Overall, impulsivity appears to be associated with exposure to several drugs of abuse and is particularly apparent when drug is withdrawn following chronic contingent or non-contingent administration.

1.4. Amygdala-related learning and memory

Stimulus-reward learning occurs via a Pavlovian associative mechanism that is regulated by the amygdala (McDonald and White, 1993; Kantak et al., 2001). In adult rats trained to self-administer cocaine or receiving yoked-cocaine passively, stimulus-reward learning was disrupted as assessed by preference for a cue paired with a highly palatable food reward (Udo et al., 2004; Kerstetter and Kantak, 2007). Chronic amphetamine injection also has been shown to impair

amygdala-dependent appetitive cue learning (Ito and Canseliet, 2010).

Pavlovian cued fear conditioning also measures amygdala-related learning, but in this case, learning is induced by negative rather than positive affect (Maren et al., 1996; Campeau and Davis, 1995). Acute or chronic injection of morphine (Good and Westbrook, 1995; Gu et al., 2008) and cocaine (Wood et al., 2007; Burke et al., 2006) have been shown to impair acquisition and extinction of cue-conditioned fear in rats. Acute ethanol injection (Lattal, 2007; Land and Spear, 2004) and withdrawal from its chronic oral consumption (Bergstrom et al., 2006) also impair acquisition and extinction of cue-conditioned fear in rats. Chronic nicotine injection on the other hand, can impair extinction but not acquisition of cue-conditioned fear (Tian et al., 2008) whereas chronic amphetamine injection can enhance acquisition but not extinction of cue-conditioned fear (Carmack et al., 2010). Collectively, these studies demonstrate mainly impairment in amygdala-related learning following contingent and non-contingent exposure to various drugs of abuse in animal subjects.

1.5. Hippocampus-related learning and memory

The hippocampus is involved in the processing of spatial, contextual and episodic associations (Smith and Mizumori, 2006). It is important for the acquisition of new learning and for the strengthening of learned associations for later retrieval (Zola-Morgan and Squire, 1990; Morris et al., 2006). Using either a water maze task of spatial learning (Del Olmo et al., 2007) or a radial-arm maze task of spatial learning (Kantak et al., 2005), adult rats self-administering cocaine or receiving it passively in a yoked fashion were shown to reach their goal (finding a hidden platform or retrieving all eight rewards) more quickly than saline controls when tested 0.5 to 3 h after cocaine sessions ended. It is possible that these findings are explained by the psychomotor stimulant effects of cocaine and do not reflect an actual improvement in spatial learning. Alternatively, cocaine-induced deficits in the functioning of the prefrontal cortex and amygdala could cause other memory systems, such as the hippocampus, to gain greater control over behavior (White and McDonald, 2002; Poldrack and Packard, 2003). Whether or not this abnormally rapid processing of spatial information in cocaine-exposed rats is maladaptive remains to be determined. It should be noted, however, that one study using experimenter-delivered, high-dose injection of cocaine (40 mg/kg/day, s.c.) found increased escape latencies (worse performance) in the water maze task (Quirk et al., 2001). This is consistent with studies in rats exposed to experimenter-delivered, high-dose injection of cocaine (50 mg/kg/day, s.c.) during the preweaning period and then tested on a radial-arm maze task during adulthood in the drug-free state (Melnick et al., 2001). These findings argue against simple psychomotor activation as an explanation for improved performance in spatial learning tasks following i.v. cocaine exposure. Dose may be a critical factor for observing cocaine-induced improvements or deficits in spatial learning in rats because in the i.v. cocaine studies mentioned above (Del Olmo et al., 2007; Kantak et al., 2005), the cumulative dose of cocaine was approximately 10 to 15 mg/kg/day, with its i.v. delivery spaced over a 2-hr period. The rats receiving a single 40 mg/kg/day s.c. injection of cocaine (Quirk et al., 2001) would have had higher sustained blood levels of cocaine at the time of testing relative to the rats in the self- and passive-administration studies.

Concerning other drugs of abuse, chronic heroin injection in prenatal and adult mice (Tramullas et al., 2008; Wang and Han, 2009), chronic high dose nicotine infusion via minipump in adult rats (Scerri et al., 2006), and acute ethanol injection in adolescent and adult rats (Silvers et al., 2003) also were shown to produce deficits in spatial learning. Similar to cocaine, one recent study has shown that while chronic amphetamine injection impaired amygdala-dependent appetitive cue learning, it enhanced hippocampus-dependent spatial learning (Ito and Canseliet, 2010).

Like spatial learning, contextual learning is impaired by drugs of abuse in animal models of contextual fear conditioning, which requires the hippocampus (Rudy et al., 2004). Acute and chronic injection of cocaine (Wood et al., 2007; Morrow et al., 1995) has been shown to attenuate acquisition of contextual fear conditioning. Chronic morphine injection also attenuates acquisition of contextual fear conditioning when tested early but not later in withdrawal (Gu et al., 2008; McNally and Westbrook, 2003). Whereas acute nicotine injection in low doses has been shown to enhance acquisition of contextual fear conditioning (Wehner et al., 2004), its is disrupted following chronic nicotine withdrawal (Gulick and Gould, 2008). Acute ethanol injection has unique effects on contextual fear conditioning; high doses impair and low doses enhance its acquisition (Gulick and Gould, 2007; Wehner et al., 2004). Given that high doses of ethanol have anxiolytic actions (Aston-Jones et al., 1984), it is possible that the reduction in freezing behavior in a fear-related context by high dose ethanol is mediated by an anxiolytic effect rather than by a disruption in contextual learning. Nicotine, which also has anxiolytic effects (Cohen et al., 2009), interacts with ethanol in such a way to suggest that high dose ethanol reduces freezing behavior by disrupting contextual learning. Specifically, high dose ethanol-induced deficits in contextual fear conditioning are reversed by acute low dose nicotine injection (Gulick and Gould, 2008). Moreover, acute low dose ethanol injection can cause a reversal of high dose nicotine withdrawal-induced deficits in contextual fear conditioning (Gulick and Gould, 2008). Collectively, these studies demonstrate that various aspects of hippocampus-related learning are altered following contingent and non-contingent exposure to drugs of abuse or their withdrawal in animal subjects. Dose may be a critical factor for observing deficits or improvements in hippocampus-related learning.

Given the above changes in attention, working memory, impulsivity and associative learning, it appears that functioning of the prefrontal cortex, amygdala and hippocampus is altered by chronic exposure to drugs of abuse. Whether these changes described above are associated with development of the addicted state or are related simply to long-term contingent or non-continent drug exposure remains a question for future investigations. The value of these animal studies is that they help us understand how functioning of key structures important for extinction learning (see below), may be impacted by chronic exposure to drugs of abuse

2. Neurobiological substrates of drug cue extinction learning

In order to develop effective pharmacotherapies for use in combination with exposure therapy in the treatment of drug addiction, it is crucial to understand the neurobiological underpinnings of drug cue extinction learning. While research on this topic in the addiction field is still in its infancy, evidence indicates that drug cue extinction may involve circuits and use mechanisms of synaptic plasticity similar to those of conditioned fear learning (Myers and Carlezon, 2010b for review). Two animal paradigms are routinely employed to assess addiction-related extinction learning at the preclinical level: the conditioned place preference and drug self-administration procedures.

Conditioned place preference is used to assess the ability of non-contingent or passive administration of drugs of abuse to establish learnt contextual associations and provides a measure of conditioned drug reward (Tzschentke, 2007). Using this procedure, a drug is repeatedly paired with a unique contextual environment, and over time the animal exhibits a preference for the drug-paired environment over an environment that has been paired with a neutral pharmacological stimulus (*i.e.,* saline; Carlezon, 2003). Subsequently, place conditioning can be reduced or eliminated by conducting repeated preference tests in the drug-free state (extinction training;

Bardo et al., 1986; Calcagnetti and Schechter, 1993; Mueller and Stewart, 2000; Schroeder and Packard, 2004). Thus, this procedure measures extinction to background environmental cues associated with drug exposure.

The self-administration model uses operant responding for drug delivery and measures the reinforcing effects of a drug. In this paradigm, subjects typically are trained to perform an operant task (nose poke or lever press) in order to receive an intravenous infusion of drug, serving as the unconditioned stimulus (US). Drug delivery often is paired with the presentation of a conditioned stimulus (CS), a discrete tone and/or light, which allows for the formation of Pavlovian CS–US associations. One form of extinction training involves removal of drug and discrete CSs in the self-administration environment (sometimes referred to as response extinction training). This procedure measures extinction to environmental cues associated with drug exposure and is the most widely used method of extinction training in animal self-administration studies. Response extinction training typically precedes reinstatement tests in which animals are reintroduced to the discrete cues. When the discrete cues are reintroduced, the conditioned response, *i.e.,* operant responding, is reinstated and this behavioral output is designated as drug-seeking behavior (Spealman et al., 1999). Drug-seeking behavior is analogous to cue reactivity in humans and is conceptualized as the sensitivity to drug-associated cues. These reinstatement sessions may be viewed as drug cue extinction sessions, whereby animals learn that the CS associated with the response no longer predicts delivery of primary reinforcement, resulting in a decline in drug-seeking behavior. However, it is important to consider that the use of reinstatement tests to model drug cue extinction involve the animal first undergoing response extinction training, which in itself produces marked neurobiological changes in the brain (Schmidt et al., 2001; Sutton et al., 2003; Self et al., 2004). In some instances, reinstatement tests follow a period of abstinence (removal of both the drug and the drug-paired environment) that also produces neurobiological changes (Lu et al., 2004b; Schmidt and Pierce, 2010). Both processes are not necessarily direct contributors to the learning mechanisms at work during drug cue extinction. An animal model that explicitly extinguishes responses only in the presence of discrete drug-paired cues would more closely approximate exposure therapy in drug addicts (*e.g.,* Nic Dhonnchadha et al., 2010b). Nonetheless, a review of research using these three different methods of extinction training in self-administration studies (response extinction training, reinstatement testing, drug cue extinction training), as well as extinction training associated with the conditioned place preference procedure, reveals an overlap between brain sites whose learning, memory, and executive functions are impaired by chronic drug use (see Section 1 above) and brain sites that are important for effective addiction-related extinction learning.

2.1. Basolateral amygdala

Several lines of research have extensively implicated the basolateral amygdala (BLA) in the initial formation of cocaine-cue associations, as well as expression of cocaine-seeking behavior (*e.g.,* Brown and Fibiger, 1993; Whitelaw et al., 1996; Ciccocioppo et al., 2001; Kruzich and See, 2001; Mashhoon et al., 2009). The use of c-Fos as a marker of neuronal activation indicates involvement of this area following cue-elicited drug-seeking behavior. Increased c-Fos expression was observed in the BLA following cue-elicited cocaine-seeking behavior to both an extinguished and non-extinguished cocaine-paired cue (Neisewander et al., 2000; Ciccocioppo et al., 2001; Kufahl et al., 2009). Additionally a correlation between lever pressing and c-Fos expression in the BLA was evident (Kufahl et al., 2009). Using the conditioned place preference paradigm, Miller and Marshall (2005) showed that cocaine associated environmental stimuli activate BLA neurons, as shown by increases in c-Fos expression. In addition, increased levels of c-Fos were observed in BLA during reinstatement of alcohol-seeking behavior (Millan et al., 2010).

Disruption to BLA activity via lesions or inactivation blocks the ability of cocaine associated stimuli to reinstate extinguished responding (Meil and See, 1997; Grimm and See, 2000; Kantak et al., 2002; Yun and Fields, 2003; McLaughlin and See, 2003; Peters et al., 2008b; Mashhoon et al., 2010). Conversely, electrical stimulation of the BLA reinstates conditioned response in rats subsequent to response extinction training (Hayes et al., 2003). Disruption of BLA functioning following cue-induced reinstatement sessions results in impaired consolidation of this cue extinction memory, as evidenced by poor retrieval during a subsequent cue extinction retention session (Fuchs et al., 2006b).

Using an animal model that more closely approximates cue exposure therapy in drug addicts, we recently demonstrated the importance of the BLA for cocaine cue extinction learning (Szalay et al., 2011). In this study, rats were trained to self-administer cocaine and then underwent two 1 h extinction sessions (no cocaine, but cues present). Rats received infusions of lidocaine (a neuronal inactivating agent) or vehicle bilaterally into the rostral BLA (rBLA) prior to extinction sessions to determine if this site was important for acquisition of cocaine cue extinction learning. Additional controls examined the effect of lidocaine or vehicle infused unilaterally into the rBLA. Results (Fig. 1) show that bilateral inactivation of rBLA with lidocaine slowed acquisition of cocaine cue extinction learning. The decreases in active lever responses from day 1 to day 2 of extinction training were significantly smaller after lidocaine than after vehicle. Lidocaine was ineffective in altering acquisition of cocaine cue extinction learning when unilateral rBLA manipulation was implemented. Collectively, data from a variety of studies suggest that the BLA may be important for the learning and consolidation of drug cue extinction.

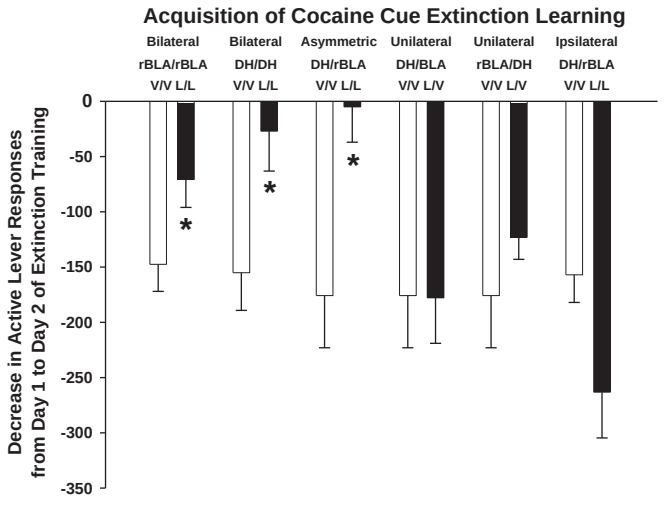

Fig. 1. Decrease in active lever responses from day 1 to day 2 of extinction training during acquisition of cocaine cue extinction learning. Rats were trained to self-administer 1.0 mg/kg cocaine under an FI 5 min (FR5:S) second-order schedule before undergoing two 1 h extinction training sessions on consecutive days for which cocaine delivery was suspended, but the cocaine-paired discrete light cue was presented upon completion of each FR5. Rats received infusion of vehicle or lidocaine into the rBLA of both hemispheres (bilateral rBLA/rBLA); infusion of vehicle or lidocaine into the DH of both hemispheres (bilateral DH/DH); infusion of vehicle or lidocaine into the DH of one hemisphere and the rBLA of the contralateral hemisphere (asymmetric DH/rBLA); infusion of vehicle or lidocaine into the DH of one hemisphere with infusion of only vehicle into the contralateral rBLA (unilateral DH/rBLA); infusion of vehicle or lidocaine into the rBLA of one hemisphere with infusion of only vehicle into the contralateral DH (unilateral rBLA/DH); infusion of vehicle or lidocaine into the DH and rBLA of the same hemisphere (ipsilateral DH/rBLA). $n = 4$–8 rats per treatment group. * $p < 0.05$ compared to the corresponding vehicle/vehicle (V/V) control treatment. The figure is adapted from Table 1, reported in Szalay et al., 2011.

2.2. Hippocampus

Several studies have shown that the dorsal hippocampus (DH) has an important role in encoding contextual information to label and retrieve memories (Rudy et al., 2002; Sanders et al., 2003) in addition to its involvement in the extinction of fear-associated memories (Wilson et al., 1995; Hartley and Phelps, 2010). Inactivation or blockade of glutamatergic neurotransmission of the DH can inhibit reinstatement of cocaine-seeking behavior (Fuchs et al., 2005; Fuchs et al., 2007; Xie et al., 2010).

In the same study reported above to examine the role of the BLA in cocaine cue extinction learning, the DH also was investigated (Szalay et al., 2011). In addition to evaluating bilateral inactivation of the DH, inactivation of the DH in one hemisphere and the rBLA in the contralateral hemisphere (asymmetric inactivation) was evaluated to determine if the serial connection between these sites on both sides of the brain was important for acquisition of cocaine cue extinction learning. Unilateral DH and ipsilateral DH/rBLA controls were used. Results (Fig. 1) show that bilateral inactivation of DH and asymmetric inactivation of DH/rBLA with lidocaine slowed acquisition of cocaine cue extinction learning. The decreases in active lever responses from day 1 to day 2 of extinction training were significantly smaller after lidocaine than after vehicle. Lidocaine was ineffective in altering acquisition of cocaine cue extinction learning after unilateral DH or ipsilateral DH/rBLA manipulations. Collectively, these findings suggest that the BLA and DH need to be functionally active simultaneously in both brain hemispheres to extinguish drug-seeking behavior.

2.3. Ventral and dorsal striatum

The ventral striatum consists of the nucleus accumbens core (NAc core) and shell (NAc shell) and is involved in the control of goal-directed behaviors (Kelley et al., 1997; Parkinson et al., 2000; Di Ciano and Everitt, 2001) and instrumental learning (Smith-Roe and Kelley, 2000). In contrast, the dorsal striatum is involved in habit learning (Wickens et al., 2007). The core region has been implicated primarily in motivated behavior that has become conditioned to particular cues, consistent with its anatomical relationships with the amygdala (Ito et al., 2004). Importantly, a distinct pattern of firing is observed in NAc cells during presentation of conditioned stimuli (Carelli et al., 2000; Ghitza et al., 2003; Nicola et al., 2004; Yun et al., 2004), an effect that persists after an extended period of cocaine abstinence (Hollander and Carelli, 2007). With respect to extinction, inactivation of the NAc core suppressed cocaine-seeking on the first day of response extinction training, and appeared to inhibit the formation of extinction memory (Sutton et al., 2003). NAc shell inactivation by contrast did not alter responding during the first extinction training session. Similar results are reported during cue-reinstatement tests whereby inactivation of the NAc core, but not NAc shell, attenuated reinstatement of cocaine-seeking behavior (Fuchs et al., 2004). However, inactivation of either the NAc core or shell failed to alter cue-induced drug-seeking behavior following a period of abstinence (See et al., 2007). These results suggest that different NAc circuitry is engaged during tests for cocaine-seeking behavior following response extinction training *vs.* abstinence from cocaine self-administration. In contrast to the NAc, inactivation of the dorsal striatum disrupts cocaine-seeking behavior following either response extinction training or abstinence from cocaine self-administration (Fuchs et al., 2006a; See et al., 2007). Collectively, these findings suggest that in the absence of drug reinforcement, the ventral striatum may be engaged to maintain goal-directed responses only in the presence of salient cues and the dorsal striatum may be engaged to maintain habitual responses even in the absence of salient cues to impact the rate of extinction. However, the role of the ventral and dorsal striatum remains unexplored in an animal model that more closely approximates cue exposure therapy in drug addicts.

2.4. Medial prefrontal cortex

A role for the medial prefrontal cortex (mPFC) in extinction has been demonstrated during cocaine cue reinstatement tests that follow abstinence, *i.e.*, when the animal is no longer exposed to cocaine or the cocaine-associated environment for a certain period of time. Using c-Fos activation methods to reveal neurosubstrates of extinction, an increase in the expression of c-Fos protein in the ventral mPFC (infralimbic and ventral prelimbic cortices) was observed during reinstatement testing in rats initially trained to self-administer cocaine before undergoing abstinence (Zavala et al., 2007). In mice trained in the conditioned place preference paradigm, cocaine associated environmental stimuli activated c-Fos in interneurons of the prelimbic cortex (Miller and Marshall, 2005). Similar changes in the expression of c-Fos in the mPFC are reported after re-exposure to environments previously paired with morphine, nicotine and ethanol (Schroeder et al., 2000; Schroeder et al., 2001; Wedzony et al., 2003).

Following a period of abstinence from cocaine self-administration, inactivation of the ventral mPFC was shown to decrease responses during a cue extinction session, while local stimulation increased responses (Koya et al., 2009). These findings are in contrast to those reported during cue-reinstatement tests conducted following response extinction training. Inactivation of dorsal mPFC (anterior cingulate and dorsal prelimbic cortices), but not ventral mPFC, was shown to attenuate cue-induced reinstatement of cocaine-seeking behavior (McLaughlin and See, 2003; Di Pietro et al., 2006; Di Ciano et al., 2007). Furthermore, Peters et al. (2008b) reported that inactivation of the ventral mPFC potentiated spontaneous recovery of cocaine-seeking four weeks after termination of response extinction training. Spontaneous recovery refers to the restoration of the extinguished response that occurs in a test session performed following a delay (Rescorla, 2004). As previously mentioned, it has been suggested that the neurocircuitry of cue-elicited responding after response extinction training is different from that after abstinence (Fuchs et al., 2006a; Peters et al., 2008a; See et al., 2007), which may explain the discrepancy in the observed results. These findings underscore the necessity of examining the role of the ventral mPFC in an animal model that more closely approximates cue exposure therapy in drug addicts.

3. Animal studies with cognitive enhancers

The fact that the potential effects of exposure therapy may be hampered by drug-induced deficits in cognitive functioning in drug addicts has led to the study of alternative approaches to compensate for these shortcomings (*e.g.,* Vocci, 2008). It is hoped that exposure therapy combined with a cognitive enhancer will prove efficacious in preventing relapse in individuals with substance use disorders. This strategy differs significantly from other approaches that attempt to generally overcome the cognitive deficits associated with drug addiction by administering cognitive enhancers to improve treatment retention and outcome (for review see Sofuoglu, 2010). There are several promising candidate cognitive enhancers for use in combination with exposure therapy, as assessed in the four preclinical models employed to study drug cue extinction (see Section 2 above).

Recent studies have shown that consolidation of drug cue extinction learning in rats and monkeys can be facilitated with systemically applied drugs targeting numerous systems. To assess the effects of putative treatment strategies, subsequent tests of cue- or drug-elicited drug-seeking behavior (to mimic reactivity to cues or drug in humans) or reacquisition (when the drug is onboard again in the presence of cues) are evaluated in animals. A common pathway of extinction-facilitating compounds may be the glutamatergic system, modulation of which can regulate synaptic plasticity and hence learning and memory processes (Martin et al., 2000). Activation of N-methyl-D-aspartate (NMDA) receptors leads to long-term potentiation and long-term depression,

which are mechanisms of synaptic plasticity associated with learning and memory formation (Kemp and Manahan-Vaughan, 2007), as well as its extinction (Quirk, 2006; Dalton et al., 2008). Thus, modulation of glutamate activity during extinction training may facilitate the process by which drug-paired cues lose salience and their control over behavior.

3.1. Glycine site agonists

To date, the glycine-binding site of the NMDA receptor has been proposed as a putative target for enhancing extinction learning. Since glutamate and direct-acting NMDA receptor agonists may be neurotoxic and are known to cause excitotoxicity (Olney, 1994; Svensson, 2000), the strategy used in the last decade has relied on drugs that enhance NMDA neurotransmission indirectly through modulatory sites on the NMDA receptor complex (Millan, 2005; Stahl, 2007). The strychnine-insensitive glycine site on the NMDA receptor complex is one such modulatory site where glycine in the presence of glutamate facilitates ion channel opening and excitatory neurotransmission without directly increasing extracellular levels of glutamate. Much success has been reported with D-cycloserine (DCS), a partial agonist at the glycine site of the NMDA receptor (Hood et al., 1989). In the animal literature, DCS has been shown to improve learning and memory in rats (Land and Riccio, 1999; Pussinen and Sirvio, 1999; Lelong et al., 2001) and monkeys (Matsuoka and Aigner, 1996; Schneider et al., 2000), as well as facilitating fear extinction learning (Davis et al., 2006; Vervliet, 2008).

Several studies have investigated the ability of DCS treatment to enhance extinction of drug-induced conditioned place preference. Systemic administration of DCS at doses of 15 and 30 mg/kg either before or immediately following 1 to 3 extinction training sessions has been shown to enhance extinction of a cocaine-associated contextual memory when testing occurs in the same context in rats (Botreau et al., 2006; Paolone et al., 2009) and mice (Kelley et al., 2007; Thanos et al., 2009). The facilitative effect of DCS administered systemically in rats could be replicated by local injections made directly into the BLA, indicating the involvement of this brain region for the acquisition and consolidation of new associations that are formed during cocaine cue extinction training (Botreau et al., 2006). Moreover, the effects of DCS were specific for extinction memory, as the magnitude of cocaine conditioned place preference (original learning) was not affected when DCS was injected during the conditioning phase rather than the extinction phase (Botreau et al., 2006). Additionally, a time-dependent facilitative effect was observed with DCS. Specifically, a 4 h lapse between termination of extinction training and DCS administration led to reduced effectiveness of the cognitive enhancer, coinciding with the theoretical time-window of NMDA-dependent memory consolidation. Notably, long-lasting effects of intra-amygdalar infusion of DCS (10 μg/μl/site) in rats and low dose systemic DCS (15 mg/kg) in mice on extinction of cocaine-conditioned place preference were evident 2 weeks after the end of extinction training sessions (Botreau et al., 2006; Thanos et al., 2009). This was not the case, however when mice were tested 1–2 weeks after termination of extinction training in combination with high dose of DCS (30 mg/kg), and actually resulted in the renewal of the conditioned place preference (Thanos et al., 2009). While these results may indicate divergent dose-dependent effects of DCS, they also highlight the importance of controlling the number of extinction and DCS treatment sessions, as it may be possible that DCS fails to provide additional benefits to extinction when the training protocols are intensive and effective in control animals (*i.e.,* longer sessions and repeated extinction training). The combination of three DCS administration and extinction training sessions prevented cocaine-primed reinstatement of the cocaine conditioned place preference in rats (Paolone et al., 2009), however, a reinstatement effect was observed in mice, with a restoration of the cocaine conditioned place preference regardless of prior DCS treatment and enhanced facilitation of extinction learning (Kelley et al., 2007).

A handful of studies have examined the effects of DCS with other drugs of abuse. Intra-hippocampal administration of DCS (10 μg/μl/site) prior to extinction training sessions facilitated the rate of extinction of amphetamine-produced place preference in rats (Sakurai et al., 2007). These results indicate the involvement of NMDA receptors in the hippocampus in amphetamine place preference extinction learning. However, when DCS was administered prior to amphetamine and context re-exposure, the extinction of the conditioned place preference was impeded, possibly due to enhancement of reconsolidation memory process (see below). In another study, administration of DCS (30 mg/kg) prior to extinction trials failed to enhance the rate of extinction of ethanol conditioned place preference in mice (Groblewski et al., 2009). The lack of effects during the extinction phase may be related to the apparent strain-dependent cognitive-enhancing effects of DCS in mice (Sunyer et al., 2008). Thus, the extinction-facilitating effects of DCS may not be evident in the DBA/2 J strain used in this study in comparison to the C57bl/c mice used in the cocaine conditioned place preference study (Thanos et al., 2009). While repeated exposure of DCS and extinction sessions (12 in total) failed to directly enhance the extinction learning process itself, this dosing regimen did however enhance the consolidation of extinction learning to impair the subsequent reacquisition (*i.e.,* when ethanol and the cues were re-introduced) of the ethanol-associated contextual memory (Groblewski et al., 2009). The finding that exposure to multiple doses of DCS before conditioning had no effect on the initial development and learning that occurs during ethanol place preference conditioning supports this result.

The conditioned place aversion paradigm in which cues are paired with drug abstinence can be used to study the withdrawal component of the conditioned response in animals. In humans, drug-paired cues elicit not only drug craving but also conditioned withdrawal, which may trigger relapse (Robbins et al., 1997). An opiate receptor antagonist such as naloxone is used to precipitate withdrawal in opiate-dependent animals, thus establishing an aversion to the withdrawal-paired compartment. Administration of DCS immediately before extinction training dramatically increases the rate of extinction of the naloxone-induced place aversion in morphine-dependent rats suggesting that extinction of conditioned drug withdrawal involves mechanisms similar to those involved in other types of drug-related extinction learning (Myers and Carlezon, 2010a).

Using an animal model that explicitly extinguishes responses only in the presence of discrete drug-paired cues and more closely approximates exposure therapy in drug addicts, administration of DCS (30 mg/kg) either before or immediately after a single extinction training session of cocaine-associated cues resulted in facilitation of extinction learning and subsequent delay in reacquisition of cocaine self-administration in rats (Nic Dhonnchadha et al., 2010b). The effects of DCS were dose-dependent, time-dependent and specific to its coupling with explicit extinction training. Employing similar conditions, pretreatment with DCS (10 mg/kg) failed to alter cocaine cue extinction learning in monkeys; however, subsequent reacquisition of cocaine self-administration was deterred. This effect of DCS was dose-dependent and specific for reacquisition of cocaine self-administration following extinction training as pretreatment with DCS prior to a self-administration control session did not reduce cocaine self-administration during the session or alter subsequent reacquisition. These results suggest that DCS augmented consolidation of extinction learning to deter reacquisition of cocaine self-administration in rats and monkeys.

In the aforementioned studies, either conditioned place preference procedure or self-administration experiments, all phases of the study (conditioning, extinction and reinstatement or reacquisition) were measured in the same context. A major drawback to exposure therapy is the context specificity of the extinction therapy normally provided in a location that is distinct from the location where drugs are typically consumed (*i.e.,* in a clinic or laboratory). This results in the restoration of

cue reactivity in the natural environment (*i.e.,* renewal effect, see Section 4). To address this issue experimentally, Torregrossa et al. (2010) extinguished lever responses in the cocaine self-administration conditioning environment (context A) and exposed the rats to two Pavlovian cue extinction sessions (60 non-contingent cue presentations were presented in the absence of levers on two consecutive days) in context B. This models the common forms of cue exposure therapy conducted in humans that involves viewing cues without overt instrumental actions. DCS (15 mg/kg) was administered on completion of each of the Pavlovian cue extinction sessions. When rats were tested in the drug-taking context, DCS-treated rats demonstrated reduced cue-reinstatement. This effect seems to be mediated by the NAc core, and reinstatement is only reduced when DCS is given in conjunction with explicit extinction learning. This study illustrates the ability of DCS to enhance the context-independent consolidation of cocaine cue extinction learning and inhibit the renewal effect of re-exposure to cocaine-associated cues.

Finally, low dose administration of DCS (5 mg/kg) prior to 2 extinction sessions in ethanol self-administration studies facilitated extinction learning in rats (Vengeliene et al., 2008). Repeated administration of DCS in combination with the extinction sessions for a total of 12 sessions did not supplement the initial benefits of DCS on extinction learning. This regimen did reduce alcohol-primed reinstatement when tested on completion of the extinction regime. Taken together, these studies in mice, rats and monkeys suggest that DCS administration reduces the conditioned reinforcing properties of drug-associated stimuli through facilitation of the consolidation of extinction learning and deters relapse to drug-seeking behavior.

Based on this success, analogs of DCS or other systemically effective glycine site modulators also are under investigation. D-serine, which is an agonist at the glycine site has been found to rescue impaired long-term potentiation and NMDA-mediated synaptic potentials in aged rats *ex vivo* (Mothet et al., 2006) as well as attenuate memory deficits induced by phencyclidine or by lesions of the perirhinal cortex *in vivo* (Andersen et al., 2003; Andersen and Pouzet, 2004). D-serine has been shown to facilitate response extinction learning at relatively low doses (100 mg/kg) that subsequently reduced cocaine-primed reinstatement of drug-seeking behavior in rats trained to self-administer cocaine (Kelamangalath et al., 2009). However, in many cases the doses required to improve memory deficits *in vivo* are quite high (500–1000 mg/kg s.c.) and are well within the range that induces nephrotoxicity in rats (Maekawa et al., 2005). The nephrotoxic effects of D-serine were not observed in mice, guinea pigs, rabbits, dogs, and gerbils (Kaltenbach et al., 1979) and analysis of kidney function parameters did not reveal any abnormalities in the majority of clinical trials (Tsai et al., 1998; Lane et al., 2005; Heresco-Levy et al., 2005), although see Kantrowitz et al. (2010). Administration of D-serine may be of therapeutic value as a pharmacological adjunct to exposure therapy, however, in humans large gram-level doses of ~2 g/day must be employed in order to significantly elevate central nervous system levels and penetrate the blood-brain-barrier (Javitt, 2008). Additionally, efficacy and side effect profile of higher doses has not been systematically explored (Kantrowitz et al., 2010), consequently agents targeting other means of selectively modulating the NMDA receptor glycine site may be a more appropriate route to follow.

3.2. Glycine-transporter inhibition

Another strategy is to increase glycine levels and hence NMDA functioning via the use of a glycine transporter-1 (Gly-T1) inhibitor. Gly-T1 is located on glial cells and its reuptake pump is the main route of inactivation of synaptic glycine. Therefore, the inhibition of Gly-T1 reuptake can increase glycine levels in glutamatergic synapses and consequently augment NMDA-receptor transmission (Stahl, 2007). Rodent studies have shown amelioration of phencyclidine-induced cognitive deficits after treatment with the Gly-T1 inhibitor NFPS (Hashimoto et al., 2008), a synthetic derivative of sarcosine (Nmethylglycine), the endogenous inhibitor of GlyT1 (Bergeron et al., 1998; Herdon et al., 2001). Similarly, MK-801-induced impairments in long term potentiation, reference memory (Manahan-Vaughan et al., 2008) and novel object recognition (Karasawa et al., 2008) is reversed by NFPS treatment. Moreover, Gly-T1 inhibitors (ALX-5704 and Org 24598) ameliorate deficits in prepulse inhibition of the acoustical startle response in mice and reverse phencyclidine induced hypermotility, stereotypy and ataxia (Brown et al., 2001; Kinney et al., 2003). In nonhuman primates, pretreatment with the Gly-T1 inhibitor, PF-3463275 alleviated spatial working memory deficits in an acute ketamine model of cognitive dysfunction (Roberts et al., 2010). These findings indicate that targeting Gly-T1 may be beneficial for improving the cognitive function in hypoglutamatergic states, resulting from impaired NMDA receptor transmission.

To assess potential benefits of a Gly-T1 inhibitor for facilitating exposure therapy targeting drug-related cues, it was shown that administration of RO 4543338 (30 and 45 mg/kg) in combination with 3 weekly 1 h extinction training sessions facilitated cocaine cue extinction learning and deterred subsequent reacquisition of cocaine self-administration in rats (Nic Dhonnchadha et al., 2010a). The multiple doses of RO 4543338 were well tolerated and failed to produce any non-specific behavioral deficits. In this experiment, RO 4543338 facilitated the rate of extinction, as reflected in rapid loss of responding after a single extinction trial. The persistence of extinction eliminated reacquisition of cocaine self-administration. The use of multiple extinction sessions in conjunction with repeated dosing of RO 4543338 may underlie the longer lasting attenuation of reacquisition observed with the GlyT1 inhibitor relative to the effects observed with DCS (Nic Dhonnchadha et al., 2010b). These studies support the validity of the concept that enhancing NMDA receptor activity by increasing synaptic glycine levels serves to enhance drug cue extinction learning.

3.3. Cystine-glutamate exchanger activation

The cystine-glutamate exchanger is another target for potential pharmacotherapy for enhancement of drug cue extinction learning. The cystine-glutamate exchanger, which exchanges extracellular cystine for intracellular glutamate, is downregulated after chronic cocaine, resulting in reduced extracellular levels of glutamate (Baker et al., 2003a; Madayag et al., 2007; Knackstedt et al., 2009). Acute administration of the nutritional supplement N-acetylcysteine or NAC (60 and 600 mg/kg, i.p.) restored the function of the cystine-glutamate exchanger and increased the basal levels of extracellular glutamate in the nucleus accumbens after withdrawal from cocaine self-administration in rats (Baker et al., 2003b). Administration of NAC has been shown to reverse memory impairment in rats exposed to cadmium, as measured in the inhibitory avoidance task (Goncalves et al., 2010) and improve cognitive functioning in dementia patients (Adair et al., 2001).

In a study examining heroin self-administration (Zhou and Kalivas, 2008), daily NAC (100 mg/kg) facilitated extinction learning, an effect most apparent during the first 5 days of response extinction training. Fifteen days of NAC pretreatment in combination with daily response extinction training reduced cue-and heroin-elicited reinstatement. The reduction in cue-elicited reinstatement was long lasting, as a reduction was still evident after 40 days of abstinence without further NAC or extinction training. These effects may be due to the up-regulation of the cysteine-glutamate exchanger and restoration of glutamate transmission (Haugeto et al., 1996) to enhance, in this instance, heroin cue extinction learning.

Thus, use of this compound as a potential for treatment in addicts is supported by these preclinical studies in conjunction with a recent pilot study examining cue-induced cocaine craving (LaRowe et al., 2006; 2007). Following four doses of NAC (600 mg), administered at

12-hour intervals, a reduction in the subjective reports of the desire to use and interest in cocaine was reported without effecting cocaine craving, following exposure to cocaine-related cues. While this study did not specifically use the strategy of NAC in combination with exposure therapy, these results are promising and support further investigation of the effects of NAC in combination with extinction training in the clinical population.

3.4. Metabotropic glutamate receptor activation

Other strategies aimed at pharmacologically enhancing NMDA receptor function involve targeting the metabotropic glutamate (mGlu) receptors. mGlu receptors are structurally and biochemically coupled to NMDA receptors to influence NMDA receptor function and NMDA-dependent synaptic plasticity and learning and memory processes (Anwyl, 2009; Niswender and Conn, 2010; Rosenbrock et al., 2010). Of particular interest have been drugs which act on the mGlu5 receptors, which are highly expressed in the mescorticolimbic regions of the brain (Abe et al., 1992; Bell et al., 2002). These compounds do not activate the mGlu5 receptor directly, but act at an allosteric site to potentiate activation by glutamate (Conn et al., 2009). Systemic administration of the mGlu5 receptor positive allosteric modulators 3-cyano-N-(1,3-diphenyl-1 H-pyrazol-5-yl)benzamide (CDPPB) and ADX47273 improved performance in a model of hippocampus-dependent spatial learning (Ayala et al., 2009). CDPPB has been shown to reverse MK-801-induced impairments in performance in behavioral flexibility tasks (Darrah et al., 2008), and improve cognition as measured by novel object recognition (Uslaner et al., 2009).

Systemic administration of CDPPB (3 and 30 mg/kg) dose-dependently facilitated extinction of cocaine-conditioned place preference (Gass and Olive, 2009). The effect was most pronounced with the highest dose of CDPPB (30 mg/kg) and was blocked by co-administration of the mGlu5 receptor antagonist MTEP or the NMDA receptor antagonist MK-801, highlighting the functional interactions between mGlu5 receptors and NMDA receptors in extinction-related learning. In a study involving cocaine self-administration (Olive, 2010), CDPPB (30 mg/kg) was administered prior to 3 daily consecutive extinction sessions, whereby cocaine was no longer available but lever pressing resulted in presentation of the cocaine-paired CS. CDBBP facilitated cocaine cue extinction learning on days 1 and 2 of extinction training. In a preliminary study from our laboratory that was designed to mimic the weekly exposure therapy sessions typically used in people, a facilitation of cocaine cue extinction learning was observed in rats trained to self-administer cocaine when CDPPB (10 mg/kg) was administered in conjunction with 3 weekly 1 h extinction training sessions (Fig. 2, panel a). Additionally, a reduction in responding during the first cocaine reacquisition session was observed (Fig. 2, panel c), with responses returning to baseline levels over the next four reacquisition sessions. This effect was observed only when CDBBB was administered in combination with explicit cue extinction training, as CDPPB did not alter responding when administered prior to cocaine self-administration sessions (Fig. 2, panel b) and did not alter subsequent reacquisition of cocaine self-administration under these control test conditions (Fig. 2, panel d). Testing with a higher dose of CDPPB (30 mg/kg) may produce more robust effects on facilitating extinction and deterring reacquisition (Gass and Olive, 2009; Olive, 2010). These studies suggest that positive allosteric modulation of the mGlu5 receptor may be a novel avenue to facilitate extinction of drug-associated memories.

4. Translational issues – lessons learned from animal studies

Animal research using combined treatment with a cognitive-enhancer and extinction training to reduce relapse to drug-seeking behavior is highly encouraging, particularly in light of the fact that the beneficial effects observed in rodents extend to non-human primates. A next step is to translate these preclinical findings to the treatment of substance use disorders. However, there are several challenges we face due to a multitude of issues that are necessary to consider for this approach to be successful (for discussion of additional translational issues, see Kantak and Nic Dhonnchadha, 2011).

4.1. Beware of memory reactivation and reconsolidation

The timing of treatment with a cognitive enhancer and length of the exposure therapy sessions need to be considered carefully in clinical studies. Investigators agree that the general mechanism by which DCS in combination with extinction training reduces drug relapse is through enhanced consolidation of the newly formed extinction memory that competes with retrieval of the previously established drug memory. The theoretical time window for NMDA-dependent memory consolidation is up to 4 h post-training (Dash et al., 2004). Thus, if DCS is administered more than 4 h after extinction training, drug-seeking behavior is not attenuated (Nic Dhonnchadha et al., 2010b). A more critical concern is if the length of the extinction training session is too short. Early in extinction training, a memory reconsolidation process is initiated, which serves to restabilize and strengthen old memories following their reactivation through cue exposure (Nader, 2003). It has been demonstrated that when DCS is administered prior to a single 30 min session of non-contingent drug cue exposure in rats trained to self-administer cocaine, lever responses are elevated during a subsequent test for drug-seeking behavior (Lee et al., 2009). These findings indicate that the previously established drug memory can be enhanced if DCS is administered in combination with too brief a period of cue exposure in rats. The formation of extinction memory and its facilitation by DCS or other cognitive-enhancer may require a longer period of non-reinforced cue exposure (Pedreira and Maldonado, 2003). Preliminary findings from our laboratory suggest that greater than 60 min of non-reinforced drug cue exposure is necessary to stabilize cocaine cue extinction responses to saline-like levels in rats (Fig. 3).

In studies in which an augmentation of exposure therapy was reported for anxiety disorders (Ressler et al., 2004; Hofmann et al., 2006; Guastella et al., 2008; Kushner et al., 2007; Wilhelm et al., 2008; Otto et al., 2010), the length of exposure therapy sessions varied from 35 to 90 min. Is 35 to 90 min of drug cue exposure in addicts sufficient to avoid enhancing reconsolidation of drug memory after treatment with a cognitive-enhancing drug? It is important to note that in animal studies with DCS, the length of extinction training sessions is shorter for extinguishing fear-conditioned responses (15 to 24 min) than drug-conditioned responses (60 min or more). Unclear is the time course of the transition from memory reconsolidation to extinction consolidation upon cue exposure in people, especially those who are addicted to drugs and are drug cue reactive. We suggest that human laboratory studies are needed that manipulate length of the exposure sessions to ascertain optimal therapeutic conditions for enhancing consolidation of drug cue extinction and avoiding reconsolidation of drug memory after treatment with a cognitive enhancer. An additional strategy that has been proposed is to use a combined approach whereby a cognitive enhancer is used to facilitate consolidation of drug cue extinction and an amnesic agent is used to interfere with reconsolidation of drug memory during cue exposure (Taylor et al., 2009). While this concept is very appealing, navigating the temporal complexities inherent in this approach requires careful consideration and systematic evaluation.

4.2. Navigating spontaneous recovery, renewal, reinstatement and incubation of craving

Extinction is not unlearning, but is a form of new learning that competes with the original memory for retrieval. Consequently, after

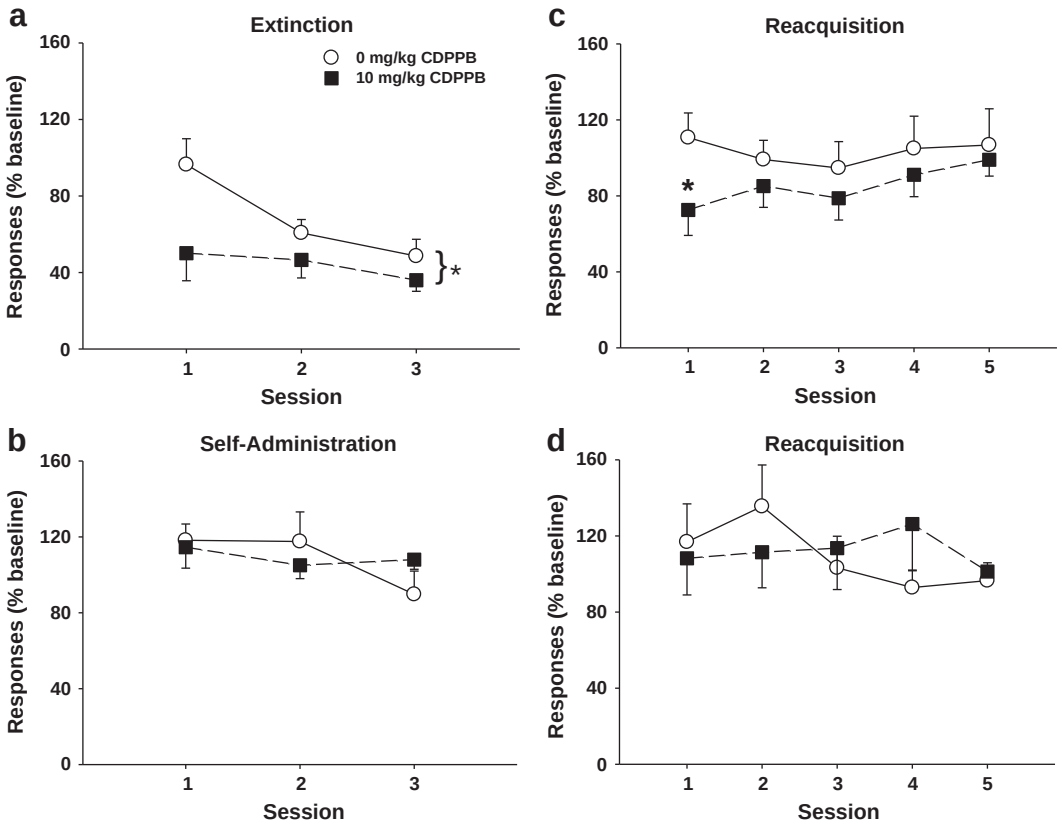

Fig. 2. Cocaine cue extinction and reacquisition of cocaine self-administration after treatment with CDPPB. Rats were trained to self-administer 0.3 mg/kg cocaine under an FI 5 min (FR5:S) second-order schedule paired with a 2-s light cue before undergoing three 1 h weekly extinction training sessions. Lever responses were extinguished by substituting saline for cocaine delivery while maintaining response contingent presentation of the cocaine-paired discrete light cue upon completion of each FR5. Rats received i.p. injections of either 0 mg/kg ($n=6$) or 10 mg/kg CDPPB ($n=6$) 15 min prior to the weekly extinction (a) or self-administration sessions (b). Reacquisition of cocaine self-administration began 7 days after the last extinction or self-administration session (c and d, respectively) under conditions identical to self-administration training. Values are the mean ± SEM percent of baseline lever responses (last five cocaine self-administration sessions). * $p<0.03$ compared to the vehicle control.

extinction training the original memory can spontaneously recover or can be renewed or reinstated. Another point to consider is incubation of craving, which may influence the long-term efficacy of exposure therapy.

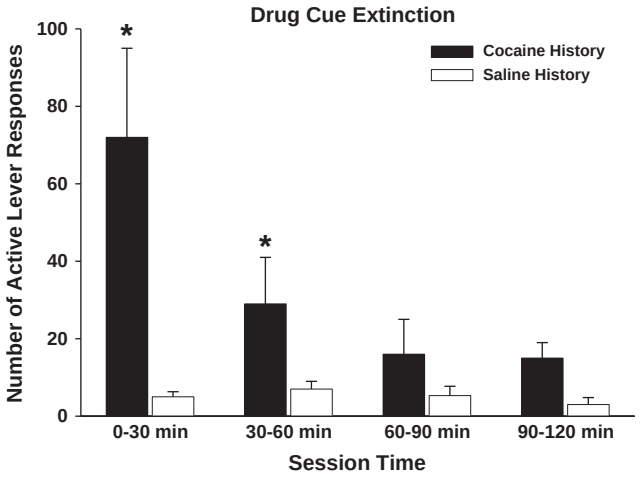

Fig. 3. Time course of drug cue extinction. Rats were trained to self-administer 0.3 mg/kg cocaine ($n=8$) or passively receive yoked saline ($n=4$) under an FR5 schedule before undergoing a single 2 h extinction training session for which cocaine delivery was suspended, but the cocaine-paired discrete light cue was presented upon completion of each FR5. The number of active lever responses during the extinction session was divided into 30 min bins. * $p<0.05$ compared to the corresponding saline control.

Spontaneous recovery of the extinguished response occurs with the passage of time, and can be viewed as a renewal effect that occurs when the CS is tested outside its temporal context (Bouton, 2004). This situation results in a failure to retrieve an extinction memory, which would be detrimental to a drug addict who has completed exposure therapy sessions and is later confronted with stimuli that can trigger a drug memory and cause relapse. Research in rats has shown, though, that when a cue is presented intermittently during extinction training, spontaneous recovery is attenuated (Brooks, 2000). Thus, just as too short a length of cue exposure during extinction training is counterproductive (leading to memory reconsolidation); too frequent the rate of cue exposure during extinction training may be equally counterproductive (leading to spontaneous recovery at later time points). It has been shown that in rats trained to self-administer cocaine under a second-order schedule before undergoing drug cue extinction, spontaneous recovery of cocaine-seeking behavior was significantly greater after 21 days than 1 day of cocaine and cocaine cue abstinence (Di Ciano and Everitt, 2002). It is important to note that the schedule of contingent cue presentation during extinction training in this study was quite frequent, which may have undermined retrieval of the extinction memory at a later time point. If exposure therapy targeting drug-related cues is to be successful, attention to the frequency of cue presentation may be an important factor for reducing spontaneous recovery. Of great interest is the fact that when DCS is combined with fear extinction training in rats, spontaneous recovery is reduced (Vervliet, 2008).

Renewal refers to the robust return of conditioned responding when there is a change of context after extinction (Bouton, 2004). The renewal effect is observed, for example, when conditioning takes

place in one context (context A) and extinction training in a second context (context B) prior to testing taking place in the original conditioning context (context A). In other words, renewal is context-specific. This situation is similar to what may be faced by individuals who become addicted to drugs in one environment, undergo exposure therapy in a therapeutic setting, and then return to their original environment. Renewal may be an obstacle to successful treatment, even if exposure therapy is combined with a cognitive enhancer. For example, DCS administration during extinction training in rats did not prevent a renewal effect from occurring when the fear-associated CS was tested in the original conditioning context (Woods and Bouton, 2006). However, in the first test for context-specificity of drug cue extinction in rats trained to self-administer cocaine (Torregrossa et al., 2010), the renewal effect was not observed in DCS-treated rats. These findings demonstrate that although DCS does not reduce context-specificity of fear extinction, it can prevent context-specificity of drug cue extinction. Further research examining the degree to which DCS and other cognitive-enhancing drugs may prevent the renewal effect for extinguished drug cues may assist in determining medication choices in individuals addicted to drugs and undergoing exposure therapy.

Reinstatement refers to the return of an extinguished response after re-exposure to the US or the CS–US complex (Bouton, 2004). In many studies of fear extinction, animals are tested for reinstatement 24 h after footshock re-exposure. For drugs of abuse, animals are tested for reinstatement immediately after drug or drug + cue re-exposure. Drug prime-induced reinstatement is thought to model relapse in abstinent addicts following drug re-exposure (de Wit and Stewart, 1981; Jaffe et al., 1989). It is of interest that reinstatement of fear following footshock re-exposure is not evident in rats that received DCS during fear extinction training (Ledgerwood et al., 2004). A lessening of the impact of reinstating stimuli by treatment with DCS and other cognitive enhancers during extinction training also has been demonstrated in cocaine-trained rats and monkeys (Kelamangalath et al., 2009; Paolone et al., 2009; Nic Dhonnchadha et al., 2010b). Collectively, these findings suggest that when exposure therapy targeting drug-related cues is provided as a stand alone treatment, addicts would remain vulnerable to relapse via spontaneous recovery, renewal and reinstatement processes. If a cognitive enhancer is combined with exposure therapy, concern for spontaneous recovery, renewal and reinstatement may be mitigated. As DCS and other cognitive enhancers also facilitate neuroplasticity in memory systems required for effective extinction learning (Rouaud and Billard, 2003; Richter-Levin and Maroun, 2010), neurocognitive impairments that may undermine exposure therapy in drug addicts may be mitigated as well.

A key factor in determining the efficacy of cue exposure therapy in combination with a cognitive enhancer may be the duration period of withdrawal or abstinence the addict has undergone prior to treatment. Numerous studies in rats, non-human primates and humans indicate that the salience of drug-related cues and hence their ability to induce drug-seeking behavior, increases in a time-dependent manner (Grimm et al., 2001; Weerts et al., 2006; Kerstetter et al., 2008; Bedi et al., 2010). This phenomenon, termed "incubation of craving" is believed to occur when most of the neuroadaptations that accompany withdrawal from chronic drug use are in progressive decline (Lu et al., 2004b). Re-exposure to drug-related cues during abstinence induces exaggerated cue reactivity, as evidenced by with an increase in extinction responding in the rat. Incubation of craving has been demonstrated to follow an inverted U-shaped curve in rats trained to self-administer cocaine, heroin, nicotine and methamphetamine (Grimm et al., 2001; Shalev et al., 2001; Lu et al., 2004a; Abdolahi et al., 2010; Shepard et al., 2004) with levels of extinction responding remaining elevated over the course of the first 3 months of withdrawal. In cigarette smokers, cue-induced craving in response to smoking cues was greater in subjects abstinent for 35 days in comparison to those that underwent 1 or 14 days or abstinence (Bedi et al., 2010). These studies indicate that the risk of relapse may persist or increase with abstinence and that the timing of extinction therapy will be an important consideration to its efficacy.

4.3. Generalizing from cocaine treatment to other drugs of abuse

As reviewed in Section 3, the majority of preclinical studies investigating the effects of cognitive enhancers on drug cue extinction have focused on cocaine as the drug of abuse. These studies have shown positive effects in that cognitive enhancers facilitated consolidation of cocaine cue extinction and attenuated relapse to cocaine-seeking and cocaine-taking behavior. Use of this strategy as a potential treatment in individuals addicted to cocaine is clearly warranted, and one group of investigators has begun to explore the effect of DCS on exposure therapy targeting cocaine-related cues in a preliminary fashion (Price et al., 2009). As these studies progress, an important point to consider is whether or not the benefits observed for DCS and other cognitive enhancers on cocaine cue extinction in preclinical studies will extend to other drugs of abuse, and in the process, provide a framework for drug abuse treatment in general.

One argument suggests this may be so, insofar as a broad spectrum of drugs of abuse (serving as USs) produces a strong associative link with discrete and contextual cues (serving as CSs) that are present in the environment at the time of drug-taking (Everitt et al., 2001). Through repeated CS–US pairings, the CS is conditioned to predict the availability the US, and forms the basis for drug memory and drug-seeking behavior. During extinction training, an organism learns that a CS no longer predicts the US, which forms the basis for extinction memory (Bouton et al., 2006). Thus, if the purpose of treatment with a cognitive enhancer is to facilitate the process by which a CS no longer predicts the US, then whichever drug of abuse is represented by the US is irrelevant. The few preclinical studies that have examined drug cue extinction and its facilitation by a cognitive enhancer support this view for drugs of abuse other than cocaine (*e.g.,* amphetamine, heroin, nicotine and ethanol).

4.4. From anxiety to addiction and back: a translational pathway for identifying new treatments

The idea that DCS might augment drug cue extinction originated from reports showing a facilitation of fear extinction after treatment with DCS in rats (Walker et al., 2002; Ledgerwood et al., 2003). These findings led to the first studies evaluating the effects of DCS combined with exposure therapy for the treatment of anxiety disorders (Ressler et al., 2004; Hofmann et al., 2006). A dual translational approach may serve as a pathway for identifying new cognitive-enhancing drugs to use in combination with exposure therapy for individuals with substance use disorders. Treatments appropriate for enhancing extinction of fear and anxiety also may be appropriate for enhancing drug cue extinction. The emergence of GlyT-1 inhibitors as treatments to enhance drug cue extinction follows this translational pathway.

One possible new treatment lead suggested by fear conditioning studies is 4-[2-(phenyl-sulfonylamino)ethylthio]-2,6-difluorophenoxyacetamide (PEPA), which is an allosteric potentiator of α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptors via an enhanced expression of GluR3/4 subunits preferentially in mPFC *vs.* amygdala or hippocampus (Zushida et al., 2007). Past work has demonstrated that chronic administration of PEPA improves Morris water maze test performance in rats made ischemic by occlusion of the middle cerebral artery (Sekiguchi et al., 2001), suggesting action as a cognitive enhancer. In fear conditioning studies in mice, PEPA administered prior to extinction training has been shown to facilitate fear extinction by reducing the duration of the freezing response during the post-extinction retrieval test (Zushida et al., 2007). These investigators additionally demonstrated that, unlike DCS, PEPA does not

facilitate reconsolidation of fear memory following brief (3 min) exposure to the fear-inducing context (Yamada et al., 2009). Recently, infusion of PEPA into the infralimbic cortex following brief (15 or 30 min) exposure to a cocaine self-administration environment was shown to enhance extinction retention (LaLumiere et al., 2010). These findings support the idea that PEPA does not facilitate reconsolidation of the drug memory even when context exposure is relatively brief during response extinction training sessions. How PEPA influences drug cue extinction learning in an animal model that more closely approximates cue exposure therapy in drug addicts remains unexplored.

A second new treatment lead concerns activation of the cannabinoid CB1 receptor. While synthetic and endogenous cannabinoids impair performance on standard tests for memory in animals (Lichtman et al., 1995; Riedel and Davies, 2005), research has shown that CB1 receptor agonists facilitate rather than impair extinction learning. Pioneering work by Marsicano et al. (2002) illustrated the importance of the CB1 receptor for extinction learning by showing impaired fear extinction in mutant mice lacking CB1 receptors. Subsequent studies in rats demonstrated that systemic administration of AM404 (an inhibitor of cannabinoid breakdown and reuptake) and WIN55212-2 (a CB1 receptor agonist) enhanced fear extinction (Chhatwal et al., 2005; Pamplona et al., 2006). Recently, both compounds were shown to not only facilitate within-session extinction of fear, but also produce long-term retention of fear extinction (Pamplona et al., 2008). Findings also support the use of CB1 receptor agonists to facilitate drug cue extinction learning. Using the conditioned place preference model in rats, administration of low doses of Δ^9-THC was shown to facilitate extinction of environmental cues associated with cocaine or amphetamine exposure (Parker et al., 2004). The use of this class of compounds with exposure therapy is made even more intriguing by findings in rats showing that intra-amygdala infusion of CB1 receptor agonists after a memory reactivation session actually blocks reconsolidation of fear memory, as well as reinstatement and spontaneous recovery of fear (Lin et al., 2006).

Another agent that has been tested in studies of fear and anxiety is the α-2 adrenergic autoreceptor antagonist yohimbine. Systemic administration of yohimbine has been shown to facilitate fear extinction in rats and mice (Cain et al., 2004; Morris and Bouton, 2007; Mueller et al., 2009) and to augment exposure therapy in individuals with claustrophobia (Powers et al., 2009). The mechanism by which yohimbine is thought to produce these effects is via noradrenergic stimulation of the mPFC. Yohimbine, though, was not able to prevent the renewal of fear when rats were tested outside the extinction context and was not able to strengthen retention of fear extinction. Preliminary evidence in rats and mice suggests that yohimbine may actually impair extinction of responses maintained by environmental cues associated with cocaine (Davis et al., 2008; Kupferschmidt et al., 2009). These findings suggest that yohimbine may not be a promising lead for augmenting drug cue extinction. Thus, treatments appropriate for enhancing extinction of fear and anxiety may not always translate into treatments appropriate for enhancing drug cue extinction.

5. Conclusions

The trajectory from drug use to addiction progresses as neural plasticity in key brain circuits plays upon the added pharmacological impact of the abused substance. The means to reverse drug-induced neural plasticity and therapeutically improve cognitive function in the addicted brain is an important quest. Preclinical studies showing the strengthening of drug cue extinction memory with DCS (summarized in Table 1) provide translational support for evaluating adjunct DCS treatment with exposure therapy in individuals addicted to drugs.

Further exploration of neurobehavioral mechanisms by which cognitive enhancers facilitate drug cue extinction is warranted. Important aspects of drug action to delineate include identifying target effector substrates, specifying anatomical localization, and revealing interactions with other neural systems. Such studies can help improve the understanding of the neurobiology of drug cue-related extinction memory and aid in the development of therapeutic agents geared to ultimately cure addiction or vastly improve the chances for recovery.

Table 1
Consequences of the effects of DCS combined with drug cue extinction training in animals.

Measure	Drug	Effect	Reference
Extinction consolidation	Alcohol	↑	Groblewski et al., 2009; Vengeliene et al., 2008
	Amphetamine	↑	Sakurai et al., 2007
	Cocaine	↑	Botreau et al., 2006
			Kelley et al., 2007
			Paolone et al., 2009
			Nic Dhonnchadha et al., 2010b
			Thanos et al., 2009
			Torregrossa et al., 2010
	Morphine WD	↑	Myers a Carlezon, 2010a
Reconsolidation	Amphetamine	↑	Sakurai et al., 2007
	Cocaine	↑	Lee et al., 2009
Reacquisition	Alcohol	↓	Groblewski et al., 2009
	Cocaine	↓	Nic Dhonnchadha et al., 2010b
Spontaneous recovery	ND		
Renewal	Cocaine	↑	Thanos et al., 2009
		↓	Botreau et al., 2006
			Thanos et al., 2009
			Torregrossa et al., 2010
Reinstatement	Alcohol	↓	Vengeliene et al., 2008
	Cocaine	↓	Paolone et al., 2009
		↑	Kelley et al., 2007

↑: Facilitation; ↓: Blockade; ND: Not determined; WD: Withdrawal.

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Conflicts of interest

Dr. Nic Dhonnchadha declares no conflicts of interest. Over the past 3 years, Dr. Kantak reports consulting fees and stock options from Yaupon Therapeutics, Inc.

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